REMARKS

Applicant submits this Amendment in response to the Office Action mailed on March 12, 2009. The application is not amended herein.

Rejections of the Claims

I. 35 U.S.C. §112, first paragraph, enablement requirement

The Examiner has rejected claims 1-16 under 35 U.S.C. §112, first paragraph, for lack of enablement of the claims to the full scope claimed. The Examiner bases this rejection on the contention that, although the specification is enabled for estriol in the claimed method, the specification does not enable the use of a selective estrogen beta receptor agonist that has a higher relative selectivity for estrogen beta receptor compared to estrogen alpha receptor than does genistein. Applicant traverses the rejection of the claims on this ground.

In the previous Amendment filed on November 30, 2008, Applicant presented arguments that showed that, in the Office Action of July 31, 2008, the Examiner had mis-characterized the invention and the predictability of the art. In the present Office Action, it is respectfully submitted that, once again, the Examiner has mis-characterized the invention and has mis-characterized the teachings of additional prior art.

Because the arguments presented in the Amendment of November 30, 2008 in response to this basis of rejection are as pertinent to the present Office Action as to the previous Office Action, Applicant repeats them here in their entirety, as follows.

Prior to the present application, it was well known in the art that estradiol was known to have favorable effects in reducing the hyperreactivity of vascular muscle cells. It was

also well known in the art that estradiol has an agonist effect on two major receptors, termed respectively the estrogen receptor α (ER-α) and the estrogen receptor β (ER-β).

It is well known in the art that, when a chemical compound, referred to as a ligand, binds to a receptor, a physiological response is triggered if the chemical compound is an agonist for the receptor. If the chemical compound is an antagonist, the binding of the chemical compound to the receptor does not trigger the physiological response and may even prevent the physiological response from being triggered. If a particular agonist ligand has high affinity for a particular receptor, then a lower concentration of the ligand is required in order to trigger the physiological response than is required of a ligand that has low affinity for a particular receptor.

Meyers, J. Med. Chem., 44:4230-4251 (2001), cited by the Examiner in the Office Action of August 9, 2007, discloses in Table 4 on page 4241 the relative affinity (selectivity) of several agonists for ER-α and ER-β. The first ligand in Table 4, estradiol, has a relative affinity (selectivity) for ER-β over ER-α of 0.46. That is, estradiol is almost two times more selective for ER-α than it is for ER-β.

Table 4 also discloses the selectivity of other ER-β ligands, including genistein and DPN (diarylpropionitrile). As disclosed in Table 4, genistein has a selectivity for ER-β over ER-α of 3. That is, genistein is more than 6 times (3 / 0.46) more selective for ER-β over ER-α than is estradiol.

As disclosed in Table 4, DPN has a selectivity for ER-β over ER-α of 78. Thus, the selectivity of DPN for ER-β over ER-α is 26 times (78 / 3) more selective for ER-β over ER-α than is genistein and is 169 times more selective for ER-β over ER-α than is estradiol. It is

clear that, with a selectivity for ER-β over ER-α of 78, the agonist activity of DPN is virtually exclusively directed to ER-β and is almost not at all directed to ER-α.

The present specification provides data obtained utilizing several ER-β agonists that have a selectivity for ER-β over ER-α which is higher than that of genistein. Epiestriol has a selectivity for ER-β over ER-α of 30. Therefore, epiestriol is 10 times more selective for ER-β than for ER-α compared to genistein and is 65 times more selective for ER-β over ER-α than is estradiol. 3βAdiol, also referred to as androstane or 5α-androstane-3β,17β-diol, has a selectivity for ER-β over ER-α of 36, which is 10 times more selective for ER-β than for ER-α compared to genistein and is 78 times more selective for ER-β over ER-α than is estradiol. Estriol has a selectivity for ER-β over ER-α of 5. Therefore, estriol is 1.6 times more selective for ER-β than for ER-α compared to genistein and is 11 times more selective for ER-β over ER-α than is estradiol.

The specification provides data in the Examples that shows the effectiveness of epiestriol, DPN, 3βAdiol, and estriol in protecting against vasospasms in an art-recognized model of the human vascular system, rhesus monkeys, and in an *in vitro* model of vascular muscle cells utilizing vascular muscle cells obtained from the rhesus monkey animal model. This *in vitro* model has been shown to be predictive of the effect of a compound to reduce hyperreactivity in vascular muscle cells. See Hermsmeyer, U.S. Patent No. 6,056,972, cited by the Examiner in the Office Action of August 9, 2007.

One of skill in the art would understand from the data presented in the specification that any ER-α agonist activity of a chemical compound is not necessary in order to obtain the results called for in the present claim. The data clearly shows that the ER-β affinity of

a chemical compound alone is sufficient to reduce hyperreactivity in vascular muscle cells. Epiestriol, DPN, and 3βAdiol have many times the selectivity for ER-β over ER-α than does genistein, and estriol has almost twice the selectivity for ER-β over ER-α than does genistein.

On pages 5-7 of the present Office Action, the Examiner cites several references to establish that one cannot predict the activity of any particular ER-beta selective agonist based on results obtained by testing a relatively small number of ER-beta selective agonists. However, it is respectfully submitted that the art cited by the Examiner does not support the Examiner's contention, but rather supports the contention of Applicant that it is not the particular chemical compound that is important, but what is important is that it is an agonist of the ER-beta receptor. Because the ER-beta receptor, when activated, produces certain results, any agonist of ER-beta will produce these results.

One reference cited by the Examiner is Lahm et al, Am. J. Physiol. Regul. Integr. Comp. Physiol., 295:R1486-R1493 (2008). Lahm conducted experiments to determine the effects of ER-alpha and ER-beta agonists on pulmonary arterial vasculature. In order to determine the effects of these agonists, Lahm utilized a single ER-alpha agonist, propylpyrazole triole (PPT), and a single ER-beta agonist, diarylpropionitrile (DPN). See page R1487, first column, paragraph before "Materials and Methods."

In the Discussion section of the article that followed the Results, Lahm uses the results based on a single ER-alpha selective agonist and a single ER-beta selective agonist to characterize the effects of activation of ER-alpha and ER-beta, respectively. In the entire Discussion section from page R1490, top of second column, to page R1492, Lahm characterizes

the effects of activation of ER-alpha and ER-beta based upon results obtained with a single agonist of each of these receptors.

Another reference cited by the Examiner is Harris et al, Endocrinology, 144(10):4241-4249 (2003). The Examiner states, on page 7 of the Office Action, that:

> According to Harris et al's studies, not all selective ER-beta agonists have the same properties. In fact the compound, ERB-041 is inactive in a large panel of estrogen responsive models and does not prevent bone loss or weight gain after ovariectomy and may not be useful in hormone therapy. Accordingly, it is unpredictable that all ER-beta selective agonists would reduce vascular hyperreactivity in vascular smooth muscle cells and be in concert with the hormone replacement therapy.

As with Lahm, Applicant respectfully submits that the above is a mis-characterization of the teaching of Harris.

In the Abstract, Harris states that a second estrogen receptor called ER-beta was discovered in 1996 and states that the physiological role of this receptor in mediating estrogen activities remains unclear. Therefore, Harris conducts a study, described in the article, to determine the effects of ER-beta.

The study is conducted using one ER-beta agonist, referred to as ERB-041. From the results of the study using this single ER-beta agonist, Harris concludes that ER-beta does not mediate the bone sparing activity of estrogen and it does not affect ovulation or ovariectomy-induced weight gain. However, ER-beta has a dramatic effect on inflammatory bowel disease and in arthritis. Based on this single ER-beta agonist, Harris concludes the Abstract by stating that the data suggests that one function of ER-beta may be to modulate the immune response.

On page 4242, last paragraph before "Materials and Methods," Harris states that:

> We describe here the biological profile of a highly selective, orally active ER-beta agonist that is representative of a family of compounds that we have studied. We characterized this compound in numerous animal models and report that its biological profile is radically different from that of nonselective or ER-alpha selective ligands. Specifically, our data suggest that an ER-beta-selective ligand will not be useful for hormone therapy or as a contraceptive agent. However, this compound has a dramatic beneficial effect in two models of inflammation involving different organ systems: the HLA-B27 transgenic rat model of inflammatory bowel disease and adjuvant-induced arthritis in the Lewis rat. These data, coupled with a lack of activity on uterus and mammary tissue, suggest that ER-beta-selective ligands may be novel antiinflammatory agents with significant therapeutic value for treating intestinal and joint inflammation.

On page 4243, first column, immediately after "Results," Harris determined that ERB-041 is a highly selective agonist for ER-beta, with a selectivity for ER-beta that is 200 times that of estradiol. On page 4243, second column, Harris tested ERB-041 and found that it is inactive in classic models of estrogen action due to a relative lack of ER-alpha agonist activity. In contrast, estradiol, which has both ER-alpha and ER-beta activity, but which is more potent on ER-alpha, is active in classic models of estrogen activity.

Like Lahm, Harris concludes the article in the Discussion section by generalizing the findings of a particular ER-beta agonist to all ER-beta agonists. In the first sentence in the Discussion section, on page 4245, Harris states that ERB-041 has certain activities and then states that "We therefore propose that ER-beta-selective ligands may have utility in treating chronic inflammatory diseases."

On page 4246, first column, Harris states that this article focuses on a particular ER-beta agonist, ERB-041, "but similar data were obtained for several other compounds in different chemical series." In the second column, Harris states that, "Having established that ERB-041 was a selective ER-beta agonist, we sought to use it as a tool to probe and define ER-

beta's functions." In the concluding sentence of the article, Harris states, "These results support our contention that ERB-041 and other ER-beta selective ligands may be therapeutically effective in the treatment of inflammatory bowel disease and/or arthritis."

It is important to understand that what is causing a biological effect due to an ER-beta agonist is not the direct effect of the ER-beta agonist itself. Rather, the ER-beta agonist binds to an ER-beta receptor, and it is this receptor, bound to an agonist, that causes effects within the body. Thus, the actual compound that is the ER-beta agonist is not what is important. Rather, what is important is only the fact that a particular compound is a selective ER-beta agonist.

The present application is based on the discovery that the ER-alpha receptor is not needed in order to reduce vascular hyperreactivity. Rather, a selective ER-beta agonist may be used for this purpose. ER-beta agonists do not, as disclosed in Harris, produce effects such as in the uterus or to induce ovulation that are produced with ER-alpha selective agonists or non-selective (both ER-alpha and ER-beta) agonists.

The Examiner states that undue experimentation would be necessary to practice the invention utilizing any ER-beta specific agonist having a selectivity for ER-beta compared to ER-alpha greater than that of genistein. However, it is respectfully submitted that the Examiner is mistaken. It is submitted that, not only is undue experimentation not required, but no experimentation at all is required.

Applicant has provided sufficient data to establish that estrogen beta receptor agonists that are selective for ER-β over ER-α to an extent that the ER-α component is trivial are suitable for use in the present invention. Further, the data provided that estrogen beta receptor

agonists that are more selective for ER-β over ER-α than is genistein are suitable for use in the present invention. Accordingly, Applicant submits that the rejection of claims 1-16 under 35 U.S.C. §112, first paragraph, for lack of enablement of the claims to the full scope claimed has been overcome and the Examiner is respectfully requested to withdraw the rejection of these claims on this ground.

II. 35 U.S.C. §103(a) - obviousness

A. Hermsmeyer, WO 98/37897; in view of Beaumont, Clin. Exp. Immunol., 24:455-463 (1976)

The Examiner has rejected claims 1-3, 7, 9, 10, and 13-16 under 35 U.S.C. §103(a) as being obvious in view of the combined disclosures of Hermsmeyer, WO 98/37897; and Beaumont, Clin. Exp. Immunol., 24:455-463 (1976).

Hermsmeyer discloses that administration of progesterone is useful in treating coronary arterial vasospasm. As indicated by the Examiner, Hermsmeyer does not disclose an ER-beta agonist compound to reduce vascular reactivity. Beaumont, at Table 3 cited by the Examiner, discloses that various tested steroid compounds competitively inhibited the binding of [^{3}H]-ethinyl-oestradiol by IgGλ. The inhibition by oestriol and progesterone of the binding of [^{3}H]-ethinyl-oestradiol by IgGλ was similar. From this disclosure of Beaumont , the Examiner concludes that progesterone and estriol are equivalent steroids. See the Office Action, page 10, third full paragraph, lines 4-5.

While it certainly is true that both progesterone and estriol are steroids, it is well known that progesterone and estriol (as well as other estrogens) differ greatly in their binding

affinity and in their activity. Estrogens bind primarily to estrogen receptors (ER) whereas progesterone binds primarily to progesterone receptors (PR). Estrogens promote formation of female secondary sex characteristics, stimulate endometrial growth, maintain vessels and skin, reduce bone resorption, and may increase certain cancers, such as breast cancers. Progesterone, in contrast, is the hormone of pregnancy. It converts the uterine endometrium to its secretory stage to prepare the uterus for implantation. It decreases the maternal immune response to allow for acceptance of a pregnancy. It decreases contractility of uterine smooth muscle and inhibits lactation during pregnancy. The above list of functions of these two hormones is not exhaustive, but is merely exemplary to illustrate that estrogens and progesterone are not equivalent steroids.

Applicant submits that the statement of the Examiner that Beaumont teaches the equivalence of estriol and progesterone as steroids is in error. Beaumont does not disclose that estriol and progesterone are equivalent steroids. Rather, Beaumont discloses in Table 3 that progesterone and estriol have approximately equivalent inhibition of the binding of [^{3}H]-ethinyl-oestradiol by IgGλ. This does not by any means indicate that estriol and progesterone are equivalent steroids. It is respectfully noted that this same Table 3 discloses that the inhibition of binding of [^{3}H]-ethinyl-oestradiol by IgGλ is approximately the same for estriol as it is for testosterone. It is respectfully submitted that one of skill in the art would not understand from this disclosure of Beaumont that estriol (an estrogen) and testosterone are equivalent steroids.

Hermsmeyer does not disclose or suggest that a compound that is a selective ER-beta agonist would have any effect whatsoever on reducing vascular hyperreactivity. It is submitted, therefore, that the disclosure of Hermsmeyer has no relevance to the present invention or to the issue of patentability of the present invention. Likewise, Beaumont does not disclose or

suggest that a selective ER-beta agonist would have any effect on reducing vascular hyperreactivity. It is respectfully submitted that these references are not pertinent to the present invention and that the combination of these two references does not suggest the present invention.

The Examiner is respectfully requested to reconsider and to withdraw the rejection of claims 1-3, 7, 9, 10, 13-16 as being obvious in view of the combined disclosures of Hermsmeyer and Beaumont.

B. Hermsmeyer, WO 98/37897; in view of Burghardt, Biology of Reproduction, 36:741-51 (1987); and Barkheim, Molecular Pharmacology, 54:105-112 (1998)

The Examiner has rejected claims 1-3, 5-7, 9, 10, and 13-16 under 35 U.S.C. §103(a) as being obvious in view of the combined disclosures of Hermsmeyer, WO 98/37897; Burghardt, Biology of Reproduction, 36:741-51 (1987); and Barkheim, Molecular Pharmacology, 54:105-112 (1998). Applicant traverses the rejection of these claims on this ground.

Hermsmeyer is discussed above and, because it discloses progesterone's effects on vasculature, is submitted to be not pertinent to the present application which concerns a receptor other than the progesterone receptor.

The Examiner cites Table 2 of Burghardt for its purported disclosure that progesterone, estradiol, and 3βAdiol are estrogen receptor binding ligands. However, the Examiner has misinterpreted the disclosure of Burghardt.

Table 2 on page 747 discloses that several compounds were tested for induction of gap junctions. Various estrogens were found to induce annular gap junctions in serosal and

macular gap junctions in myometrial cells. 5-Adiol and progesterone were included in the test. Neither of these compounds produced a detectable induction of annular gap junctions in either the serosal or macular gap junctions in myometrial cells.

It is respectfully submitted that the sole disclosure of Burghardt pertaining to progesterone and/or 5-Adiol is that neither of them is capable of inducing annular gap junctions in serosal or macular gap junctions in myometrial cells. The disclosure of Burghardt does not provide any suggestion that progesterone and an estrogen or progesterone and an estrogen beta-receptor agonist would have similar capabilities. Therefore, it is submitted that the disclosure of Burghardt is not relevant in any manner to the present application.

Barkheim discloses the existence of two different estrogen receptors, the estrogen alpha and the estrogen beta receptor, and further discloses that estradiol has selective alpha agonist potency and that epiestriol has selective beta agonist potency.

It is respectfully submitted that, aside from Barkheim, the cited prior art has no relevance to the present application. Barkheim is relevant because epiestriol is a estrogen beta-receptor agonist. However, the prior art, does not suggest or disclose that an estrogen beta-receptor agonist can be used successfully in a method as called for in the present claims.

Applicant submits that the invention called for in claims 1-3, 5-7, 9, 10, and 13-16 of the present application is not obvious over the combined disclosures of Hermsmeyer, Burghardt, and Barkheim, and the Examiner is requested to withdraw the rejection of these claims on this ground.

C. Hermsmeyer, WO 98/37897; in view of Burghardt, Biology of Reproduction, 36:741-51 (1987); Barkheim, Molecular Pharmacology, 54:105-112 (1998); and Shaak, U.S. Patent No. 6,228,852

The Examiner has rejected claims 11 and 12 under 35 U.S.C. §103(a) as being obvious in view of the combined disclosures of Hermsmeyer, WO 98/37897; Burghardt, Biology of Reproduction, 36:741-51 (1987); Barkheim, Molecular Pharmacology, 54:105-112 (1998), and Shaak, U.S. Patent No. 6,228,852. Applicant traverses the rejection of these claims on this ground.

The disclosures of Hermsmeyer, Burghardt, and Barkheim are discussed above and are not pertinent to the present invention. Shaak discloses that estrogen and progesterone are useful in hormone replacement therapy. It is respectfully submitted that the disclosure of Shaak does not fill in the gaps in the disclosures of Hermsmeyer, Burghardt, and Barkheim to establish a case of obviousness of claims 11 and 12.

Applicant submits that the combined disclosures of Hermsmeyer, Burghardt, Barkheim, and Shaak fail to disclose or suggest the invention called for in claims 11 and 12. Accordingly, the Examiner is requested to reconsider and to withdraw the rejection of these claims for obviousness.

D. Hermsmeyer, WO 98/37897; in view of Burghardt, Biology of Reproduction, 36:741-51 (1987); Barkheim, Molecular Pharmacology, 54:105-112 (1998); and Meyers, J. Med. Chem., 44:4230-4251 (2001)

The Examiner has rejected claim 8 under 35 U.S.C. §103(a) as being obvious in view of the combined disclosures of Hermsmeyer, WO 98/37897; Burghardt, Biology of Reproduction, 36:741-51 (1987); Barkheim, Molecular Pharmacology, 54:105-112 (1998), and Meyers, J. Med. Chem., 44:4230-4251 (2001). Applicant traverses the rejection of these claims on this ground.

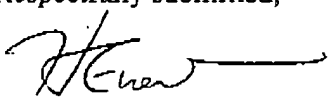
The disclosures of Hermsmeyer, Burghardt, and Barkheim are discussed above and are not pertinent to the present invention. Meyers is cited for its disclosure that diarylprionitrile (DPN) is an estrogen beta-receptor agonist. It is respectfully submitted that the disclosure of Meyers does not fill in the gaps in the disclosures of Hermsmeyer, Burghardt, and Barkheim to establish a case of obviousness of claims 8, and that the combination of disclosures of these references does not suggest the presently claimed invention.

Accordingly, the Examiner is requested to reconsider and to withdraw the rejection of claim 8 for obviousness in view of the combined disclosures of Hermsmeyer, Burghardt, Barkheim, and Meyers.

CONCLUSION

Applicant submits that the claims, as amended herein, are in condition for allowance and requests an early notice to that effect. Applicant submits a Request for Continued Examination, with applicable fees, with this Amendment.

Respectfully submitted,



Howard M. Eisenberg
Reg. No. 36,789
1220 Limberlost Lane
Gladwyne, PA 19035
Attorney for Applicant
Tel: (484) 412-8419

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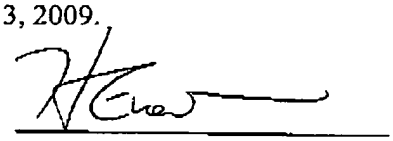

Howard M. Eisenberg